RCE 1600

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Request For Continued Examination (RCE) Transmittal

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Application Number	10/010,283
Filing Date	November 13, 2001
First Named Inventor	Carl-Axel Bauer et al.
Group Art Unit	1617
Examiner Name	Jennifer M. Kim
Attorney Docket Number	06275-150003

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This is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. §1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s)

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendment filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☒ Enclosed

      i. ☐ Amendment/Reply

      ii. ☒ Affidavit(s)/Declaration(s)

      iii. ☒ Information Disclosure Statement (IDS)

      iv. ☒ Other Submission Under 37 CFR §1.114

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. §1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. §1.17(i) required)

   b. ☐ Other _____

3. Fee The RCE fee under 37 C.F.R. §1.17(e) is required by 37 C.F.R. §1.114 when the RCE is filed.

   a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 06-1050

      i. ☐ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☒ Other Any deficiencies

   b. ☒ Check in the amount of $ 770 enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY OR AGENT REQUIRED

Name (Print/Type)	Janis K. Fraser, Ph.D., J.D.	*Registration No. (Attorney/Agent)*	34,819
Signature	Allyson R. Hatton Reg No. 54,154	*Date*	March 1, 2004

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Name (Print/Type)	Lisa G. Gray		
Signature	Lisa G. Gray	*Date*	March 1, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Carl-Axel Bauer *et al.* Art Unit : 1617
Serial No. : 10/010,283 Examiner : Jennifer M. Kim
Filed : November 13, 2001
Title : NEW USE FOR BUDESONIDE AND FORMOTEROL

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SUBMISSION UNDER 37 C.F.R §1.114(c)

Applicants submit the following new evidence and arguments. This information accompanies a request for continued examination submitted under 37 C.F.R. §1.114 subsequent to receipt of the Examiner's Answer in the pending appeal to the Board of Patent Appeals and Interferences. Applicants respectfully request that prosecution be reopened so that the Examiner may consider this new information.

At the time of this submission, claims 9 and 11-25 remain rejected under 35 U.S.C. §103(a) as being obvious in view of Carling *et al.* (WO 93/11773), in view of Cazzola *et al.* (Ref. U), and Nederland Tijdschrift Voor Geneeskunde (Ref. V), in view of Saunders Manual of Medical Practice (Ref. W). Applicants' claims are directed to methods of treating a patient suffering from COPD using a combination of formoterol and budesonide in a ratio of from 1:2500 to 12:1.

Applicants maintain that in light of the prior art at the time the invention was made there would not have been a reasonable expectation of success regarding the treatment of COPD with a combination of budesonide and formoterol. Carling *et al.* does not teach or suggest that the combination of formoterol and budesonide described therein is suitable for treating COPD. Instead, Carling *et al.* states that his combination of formoterol and budesonide is suitable for.

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treating "asthma and other respiratory disorders"; the only specific respiratory disorder mentioned is asthma. As explained in the Declaration of Jan Trofast, submitted herewith, the recitation of Carling *et al.* of "other respiratory disorders," was meant by Carling and his co-inventors (one of whom was Dr. Trofast) to include only other respiratory disorders similar to asthma, *i.e.*, disorders of bronchospastic nature (see Declaration of Jan Trofast, paragraph 5). This phrase "other respiratory disorders" was not intended to encompass all known respiratory disorders, nor would it have been so understood by the artisan.

Carling *et al.*, at page 1, lines 10-13 states that the invention "relates to the use of a bronchodilator in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as asthma" (emphasis added). There exist a number of respiratory disorders that are similar to asthma in both their pathophysiological features and their treatment protocol, for example extrinsic atopic asthma, extrinsic non-atopic asthma, intrinsic asthma, wheezing in children, and bronchospastic cough. In some cases, these disorders are referred to collectively as "asthma," but because they are different conditions, those having skill in the art of respiratory disorders, and asthma in particular, will often refer to these conditions as "asthma and other respiratory disorders." The declaration by Dr. Trofast states that this was indeed the meaning intended by Carling *et al.* (see the Declaration at paragraph 6).

Applicants previously submitted arguments addressing the many differences between asthma and COPD. To further emphasize further this point, Applicants submit Barnes *et al.* (*Eur. Resp. Jour.* 22:874-875, 2003). Barnes *et al.* states at page 672, column 2, and page 673, column 1:

> COPD is characterized by acceleration in the normal decline of lung function seen with age. The slowly progressive airflow limitation leads to disability and premature death and is quite different from the variable airway obstruction and symptoms in asthma, which rarely progress in severity. While COPD and asthma both involve inflammation in the respiratory tract there are marked differences in the nature of the inflammatory process, with differences in inflammatory cells, mediators, response to inflammation, anatomical distribution and response to anti-inflammatory therapy [emphasis added].

Applicants also submit Buist ("Definitions," in Asthma and COPD, Barnes *et al.*, eds. London: Academic Press, 2002, pages 3-6). According to Buist (page 3, column 1), the Expert Panel 2 Report (the current U.S. asthma guideline) defines asthma as:

> a chronic inflammatory disorder of the airways...In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough...These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment...[emphasis added].

Thus, a key pathophysiological feature common to asthma-related disorders is reversible airflow obstruction, which is monitored by spirometry or measurements of peak expiratory flow rate. These disorders are treated in similar fashion. They differ significantly, both in their pathophysiological features and their modes of treatment, from the wide range of non-asthma-like respiratory disorders listed above and in the medical literature. Thus, for example, these disorders differ significantly in both their pathology and their treatment from unrelated respiratory disorders such as lung cancer or asbestosis.

Buist further reports the definition of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines: "A disease state characterized by progressive development of airflow limitation that is not fully reversible..." (Buist, page 3, column 1). At page 4, column 1, he states:

> Perhaps the single most important difference between the two diseases is the nature of the inflammation: it is primarily eosinophilic, CD4-driven in asthma and neutrophilic, CD8-driven in COPD...There is ample evidence now that inhaled corticosteroids are effective against the eosinophilic inflammation that is characteristic of asthma...but largely ineffective against the primarily neutrophilic inflammation seen in COPD...

This evidence supports Applicants' assertion that COPD would not be considered to be a respiratory disorder similar to asthma by those of skill in the art.

As is explained in Dr. Trofast's declaration (paragraphs 5 and 8), the Carling *et al.* inventors did not mean to suggest that the combination of budesonide and formoterol could be

used to treat any disorder that could be generally classified in the medical literature as a "respiratory disorder." Nor would one of ordinary skill in the art have been likely to so interpret Carling *et al.* at the time of Applicants' invention. If the phrase "other respiratory disorders" were interpreted to include COPD, as urged by the Examiner, then the phrase "other respiratory disorders" would also refer to every other respiratory disorder known to man, including, but not limited to, respiratory infections such as tuberculosis and bronchopulmonary aspergillosis, cough, asbestos-related disease, different forms of lung cancer, acute respiratory distress syndrome, toxic lung injury, cystic fibrosis, interstitial lung diseases (such as idiopathic pulmonary fibrosis and the like), alveolitis, sarcoidosis, and many other diseases and conditions involving impaired respiratory function (for a more complete list see, for example, "Respiratory Medicine," vol. 1, 3rd edition, Gibson *et al.*, eds; table of contents attached).

Assuming, *arguendo*, that the artisan had interpreted the phrase "other respiratory disorders" broadly, as urged by the Examiner, it would follow that the artisan would have considered the Carling *et al.* combination suitable for the treatment of respiratory disorders such as lung cancer and asbestosis -- a conclusion that is patently absurd. Clearly, this was not the intention of the inventors in Carling *et al.*, nor would such an interpretation have seemed reasonable to one of ordinary skill in the art at the time of Applicants' invention.

Applicants also submit Calverley *et al.* (*Eur. Resp. J.* 22:912-919, 2003), the first report of successful treatment and prevention of exacerbations in COPD patients using a combination of inhaled corticosteroid (budesonide) and β2 agonist (formoterol). Table 3 of Calverley *et al.* shows that the combination of budesonide and formoterol reduces the number of exacerbations more effectively than either budesonide or formoterol alone. Table 3 shows that the number of exacerbations per year (mean rate per patient per year) was 1.80 during treatment with a placebo and a near-equivalent 1.85 during treatment with the β2 agonist formoterol. Exacerbations were mildly reduced following treatment with the corticosteroid budesonide (1.60 mean rate per patient per year) although this decrease was still not significant as compared to treatment with a placebo. Treatment with the combination of budesonide and formoterol reduced the rate of exacerbations to 1.38, a significant reduction as compared to treatment with placebo. This result was surprising given

the low efficacy or ineffectiveness of treatment with either budesonide or formoterol alone. The authors add that "[i]t...seems that formoterol and budesonide in combination are more effective at reducing proliferation of airway smooth muscle than either drug alone, as a result of synchronised cellular signalling..." (page 918, column 2).

Rabe (*Eur. Resp. Jour.* 22:874-875, 2003; submitted herewith) is an editorial that expresses doubt regarding the appropriateness of combining long-acting $\beta 2$ agonists and corticosteroids for the treatment of COPD, even though such treatment had proven beneficial for treatment of asthma, and despite the results of the Calverley study discussed above, which demonstrated the successful treatment of COPD patients (Calverley *et al.*, 2003).

Rabe states at page 875, column 1:

> The role of steroids in the treatment of patients with asthma...is fundamentally different compared to COPD... since the perceptions of symptoms in asthma and the evidence for early intervention probably favour the use of these drugs in combination with bronchodilators in the future in even earlier stages of the disease than currently recommended. In contrast, asymptomatic COPD patients should not be treated with drugs, and this alone, amongst other considerations, clearly calls for a differentiation of these two diseases that are fundamentally different in the vast majority of patients [emphasis added].

The opinion expressed by Rabe in 2003 is an indication of the state of the art in the study of COPD that must have existed before 2003, for example as far back as 1991, 12 years before the opinion of Rabe was published and the time the Carling reference was written. Rabe states at page 874, column 1:

> We have all witnessed the heated discussions around inhaled steroids in COPD and have seen and read the data that confirm that asthma and COPD are completely different diseases, clinically and biologically. I can see the role of long-acting bronchodilators for the treatment of COPD, an issue that is already addressed in the updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines... but the use of inhaled steroids and combination therapy as in asthma? Is this a "one size fits all" strategy that is driven by commercial interests? And were we all wrong, does this mean we no longer need to differentiate between asthma and COPD...?

The strength of conviction in the words of Rabe in 2003 suggests that prior to this, and certainly 12 years earlier, when the field of COPD research was less well-developed, the success of inhaled steroids and combination therapy for the treatment of COPD would have been even less believable.

The references submitted herewith (Barnes *et al.* (2003); Buist (2002); Calverley *et al.* (2003), and Rabe (2003)) and the Declaration of Jan Trofast support the patentability of the claims in the instant application, which are directed to methods of treating a patient suffering from COPD. The references are indicative of the *current view* of those skilled in the study of respiratory disorders, and COPD and asthma in particular – many years *after* Applicants' priority date. The references provide evidence that asthma and COPD are considered to be different diseases, and that a therapeutic regimen determined to be an appropriate treatment for asthma (as described in Carling *et al.*) is even now a controversial treatment for COPD. Only the recent findings of Calverley *et al.* provide evidence (counter to the conventional wisdom) that the combination therapy is a viable treatment option. This collection of evidence supports Applicants' position that the combination described by Carling *et al.* would not have been considered to be an appropriate treatment for COPD in 1991, when Carling *et al.* was written, nor would it have been in 1998, at the time of the present invention.

Barnes *et al.*, Buist, and Rabe represent the current state of knowledge in the art. The current confusion and lack of clarity that exists in the understanding of the physiological differences and relevant treatment therapies for COPD versus asthma represent a *higher* level of understanding than that which existed in 1991, when Carling *et al.* was written, and in 1998, when the priority application relating to the present case was filed.

Thus, in light of the remarks presented above and the accompanying references and declaration, Applicants maintain that it would not have been obvious to treat COPD with a combination of formoterol and budesonide at the filing date of the instant application.

Enclosed is a $770 check for the fee for Request for Continued Examination. Any other necessary charges or credits can be applied to Deposit Account No. 06-1050, with reference to Attorney Docket No. 06275-150003.

Respectfully submitted,

Date: March 1, 2004

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